

Remarks

Claims 1-11, 13, 16, 19, and 22 are currently pending in this application and are before the Examiner for consideration.

Claim 1-11 and 13 have been rejected under 35 U.S.C. § 112, first paragraph. Claim 1 has been amended to identify amidoamino acids appropriate for use in the subject method. The terms suggested for inclusion in the claim are disclosed in paragraphs [0002] and [0005] of the specification. Reconsideration and withdrawal of the rejection in view of the amendment is respectfully requested.

Claims 2, 6, 13, 16, 19, and 22 have been rejected under 35 U.S.C. § 112, second paragraph. Claim 2 recites that the alcohol used to esterify the amidoamino acid contains a strong acid. Strong acids are understood and defined in the art as compounds that are fully ionized in protic solvents, such as water and alcohols (see attachments A and B). Such strong acids in water include hydrochloric acid, sulfuric acid and nitric acid. Alcohols can also serve as the protic solvents for strong acids. For example HCl gas dissolved in an alcohol such as methanol produces a strong acid, methanolic HCl. Methanolic HCl can also be derived through reaction of an acid chloride with an alcohol such as methanol as illustrated in the examples accompanying the disclosure. By comparison, weak acids HX' do not completely ionize in protic solvents, but rather partially ionize to give the nonionized acid HX' in equilibrium with a small amount of the ionized form. Applicants therefore submit that the scope and meaning of the limitation is clear to one skilled in the art and reconsideration and withdrawal of the rejection to the claim is respectfully requested.

Claims 5 and 6 further define the solvents used in claim 1. Each claim has been amended to identify the step of claim 1 with which it is associated.

Claim 13 incorrectly recites the claimed product is produced by the method of claim 8, where claim 8 recites a product. The claim has been amended to correct this error as well as further define the product claimed.

Claims 16, 19 and 22 each include a formula. These formulas represent repeating units in each of the claimed polymers. The subject claims have been amended to make this clear.

In view of the amendments to the claims, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Applicants believe that the claims are in condition for allowance and such action is respectfully requested.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Fundamentals of General, Organic, and Biological Chemistry

FIFTH EDITION

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Attachment A



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10.6 Acid and Base Strength

Strong acid An acid that gives up H^+ easily and is essentially 100% dissociated in water.

Dissociation The splitting apart of an acid in water to give H^+ and an anion.

Weak acid An acid that gives up H^+ with difficulty and is less than 100% dissociated in water.

Weak base A base that has only a slight affinity for H^+ and holds it weakly.

Strong base A base that has a high affinity for H^+ and holds it tightly.

Some acids and bases, such as sulfuric (H_2SO_4), hydrochloric acid (HCl), or sodium hydroxide ($NaOH$), are highly corrosive. They react readily and, in contact with skin, can cause serious burns. Other acids and bases are not nearly as reactive. Acetic acid (CH_3COOH , the major component in vinegar) and phosphoric acid (H_3PO_4) are found in many food products. Why are some acids and bases relatively "safe," but others must be handled with extreme caution? The answer lies in how easily they produce the active ions for an acid (H^+) or a base (OH^-).

As indicated in Table 10.1, acids differ in their ability to give up a proton. The six acids at the top of the table are **strong acids**, meaning that they give up a proton easily and are essentially 100% dissociated, or split apart into ions, in water. Those remaining are **weak acids**, meaning that they give up a proton with difficulty and are substantially less than 100% dissociated in water. In a similar way, the bases at the top of the table are **weak bases** because they have little affinity for a proton, and the bases at the bottom of the table are **strong bases** because they grab and hold a proton tightly.

Note that diprotic acids, such as sulfuric acid, undergo two stepwise dissociations in water. The first dissociation yields HSO_4^- and occurs to the extent of nearly 100%, so H_2SO_4 is a strong acid. The second dissociation yields SO_4^{2-} and takes place to a much lesser extent because separation of a positively charged H^+ from the negatively charged HSO_4^- anion is difficult. Thus, HSO_4^- is a weak acid.

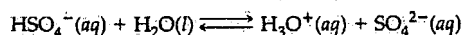
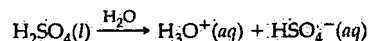


TABLE 10.1 Relative Strengths of Acids and Conjugate Bases

		ACID		CONJUGATE BASE		
Increasing acid strength ↑	Strong acids: 100% dissociated	Perchloric acid	$HClO_4$	ClO_4^-	Perchlorate ion	Little or no reaction as bases
		Sulfuric acid	H_2SO_4	HSO_4^-	Hydrogen sulfate ion	
		Hydriodic acid	HI	I^-	Iodide ion	
		Hydrobromic acid	HBr	Br^-	Bromide ion	
		Hydrochloric acid	HCl	Cl^-	Chloride ion	
		Nitric acid	HNO_3	NO_3^-	Nitrate ion	
	Weak acids	Hydronium ion	H_3O^+	H_2O	Water	Very weak bases
		Hydrogen sulfate ion	HSO_4^-	SO_4^{2-}	Sulfate ion	
		Phosphoric acid	H_3PO_4	$H_2PO_4^-$	Dihydrogen phosphate ion	
		Nitrous acid	HNO_2	NO_2^-	Nitrite ion	
		Hydrofluoric acid	HF	F^-	Fluoride ion	
		Acetic acid	CH_3COOH	CH_3COO^-	Acetate ion	
	Very weak acids	Carbonic acid	H_2CO_3	HCO_3^-	Bicarbonate ion	Weak bases
		Dihydrogen phosphate ion	$H_2PO_4^-$	HPO_4^{2-}	Hydrogen phosphate ion	
		Ammonium ion	NH_4^+	NH_3	Ammonia	
		Hydrocyanic acid	HCN	CN^-	Cyanide ion	
		Bicarbonate ion	HCO_3^-	CO_3^{2-}	Carbonate ion	
		Hydrogen phosphate ion	HPO_4^{2-}	PO_4^{3-}	Phosphate ion	
		Water	H_2O	OH^-	Hydroxide ion	Strong base

fourth edition

ORGANIC CHEMISTRY

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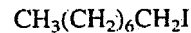
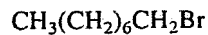
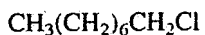
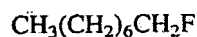
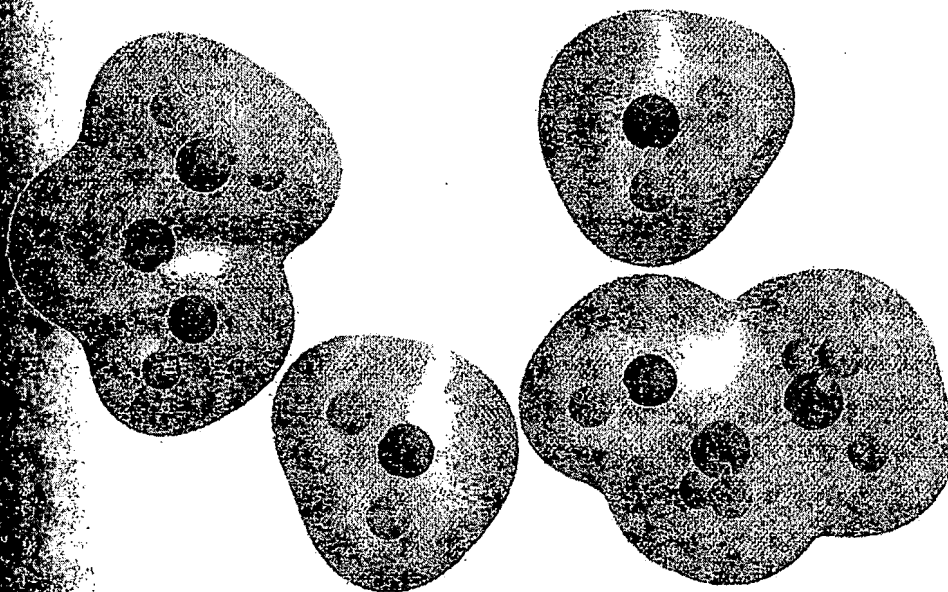
Attachment B



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FIGURE 4.5 Hydrogen bonding between molecules of ethanol and water.



Density
(20°C)

0.80 g/mL

0.89 g/mL

1.12 g/mL

1.34 g/mL

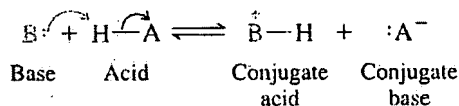
Because alkyl halides are insoluble in water, a mixture of an alkyl halide and water separates into two layers. When the alkyl halide is a fluoride or chloride, it is the upper layer and water is the lower. The situation is reversed when the alkyl halide is a bromide or an iodide. In these cases the alkyl halide is the lower layer. Polyhalogenation increases the density. The compounds CH_2Cl_2 , CHCl_3 , and CCl_4 , for example, are all more dense than water.

All liquid alcohols have densities of approximately 0.8 g/mL and are, therefore, less dense than water.

4.6 ACIDS AND BASES: GENERAL PRINCIPLES

A good understanding of acid-base chemistry is a big help in understanding chemical reactivity. This and the next section review some principles and properties of acids and bases and examine how these principles apply to alcohols.

According to the theory proposed by Svante Arrhenius, a Swedish chemist and winner of the 1903 Nobel Prize in chemistry, an acid ionizes in aqueous solution to liberate protons (H^+ , hydrogen ions), whereas bases ionize to liberate hydroxide ions (OH^-). A more general theory of acids and bases was devised independently by Johannes Brønsted (Denmark) and Thomas M. Lowry (England) in 1923. In the Brønsted-Lowry approach, an acid is a **proton donor**, and a base is a **proton acceptor**.

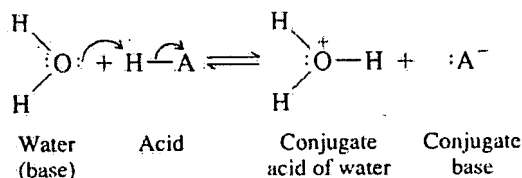


Curved arrow notation is used to show the electron pair of the base abstracting a proton from the acid. The pair of electrons in the $\text{H}-\text{A}$ bond becomes an unshared pair in the anion :A^- . Curved arrows track electron movement, not atomic movement.

The Brønsted–Lowry definitions of acids and bases are widely used in organic chemistry. As noted in the preceding equation, the **conjugate acid** of a substance is formed when it accepts a proton from a suitable donor. Conversely, the proton donor is converted to its **conjugate base**. A conjugate acid–base pair always differ by a single proton.

PROBLEM 4.6 Write an equation for the reaction of ammonia (:NH_3) with hydrogen chloride (HCl). Use curved arrows to track electron movement, and identify the acid, base, conjugate acid, and conjugate base.

In aqueous solution, an acid transfers a proton to water. Water acts as a Brønsted base.



The systematic name for the conjugate acid of water (H_3O^+) is **oxonium ion**. Its common name is **hydronium ion**.

The strength of an acid is measured by its **acid dissociation constant** or **ionization constant** K_a .

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

Table 4.2 lists a number of Brønsted acids and their acid dissociation constants. Strong acids are characterized by K_a values that are greater than that for hydronium ion (H_3O^+ , $K_a = 55$). Essentially every molecule of a strong acid transfers a proton to water in dilute aqueous solution. Weak acids have K_a values less than that of H_3O^+ ; they are incompletely ionized in dilute aqueous solution.

A convenient way to express acid strength is through the use of $\text{p}K_a$, defined as follows:

$$\text{p}K_a = -\log_{10} K_a$$

Thus, water, with $K_a = 1.8 \times 10^{-16}$, has a $\text{p}K_a$ of 15.7; ammonia, with $K_a = 10^{-36}$, has a $\text{p}K_a$ of 36. The stronger the acid, the larger the value of its K_a and the smaller the value of $\text{p}K_a$. Water is a very weak acid, but is a far stronger acid than ammonia. Table 4.2 includes $\text{p}K_a$ as well as K_a values for acids. Because both systems are widely used, you should practice converting K_a to $\text{p}K_a$ and vice versa.

PROBLEM 4.7 Hydrogen cyanide (HCN) has a $\text{p}K_a$ of 9.1. What is its K_a ? Is HCN a strong or a weak acid?

An important part of the Brønsted–Lowry picture of acids and bases concerns the relative strengths of an acid and its conjugate base. The stronger the acid, the weaker the conjugate base, and vice versa. Ammonia (NH_3) is the second weakest acid in Table 4.2. Its conjugate base, amide ion (H_2N^-), is therefore the second strongest base. Hydroxide (HO^-) is a moderately strong base, much stronger than the halide ions F^- , Cl^- , Br^- , and I^- , which are very weak bases. Fluoride is the strongest base of the halides but is 10^{12} times less basic than hydroxide ion.

TABLE 4.2 Acid Dissociation Constants K_a and pK_a Values for Some Brønsted Acids*

Acid	Formula [†]	Dissociation constant, K_a	pK_a	Conjugate base
Hydrogen iodide	HI	$\approx 10^{10}$	≈ -10	I^-
Hydrogen bromide	HBr	$\approx 10^9$	≈ -9	Br^-
Hydrogen chloride	HCl	$\approx 10^7$	≈ -7	Cl^-
Sulfuric acid	HOSO_2OH	1.6×10^5	-4.8	HOSO_2O^-
Hydronium ion	H_3O^+	55	-1.7	H_2O
Hydrogen fluoride	HF	3.5×10^{-4}	3.5	F^-
Acetic acid	CH_3COOH	1.8×10^{-5}	4.7	CH_3COO^-
Ammonium ion	NH_4^+	5.6×10^{-10}	9.2	NH_3
Water	HOH	$1.8 \times 10^{-16}\ddagger$	15.7	HO^-
Methanol	CH_3OH	$\approx 10^{-16}$	≈ 16	CH_3O^-
Ethanol	$\text{CH}_3\text{CH}_2\text{OH}$	$\approx 10^{-16}$	≈ 16	$\text{CH}_3\text{CH}_2\text{O}^-$
Isopropyl alcohol	$(\text{CH}_3)_2\text{CHOH}$	$\approx 10^{-17}$	≈ 17	$(\text{CH}_3)_2\text{CHO}^-$
tert-Butyl alcohol	$(\text{CH}_3)_3\text{COH}$	$\approx 10^{-18}$	≈ 18	$(\text{CH}_3)_3\text{CO}^-$
Ammonia	H_2N^-	$\approx 10^{-36}$	≈ 36	H_2N^-
Dimethylamine	$(\text{CH}_3)_2\text{N}^-$	$\approx 10^{-36}$	≈ 36	$(\text{CH}_3)_2\text{N}^-$

* Acid strength decreases from top to bottom of the table. Strength of conjugate base increases from top to bottom of the table.

† The most acidic proton—the one that is lost on ionization—is highlighted.

‡ The true K_a for water is 1×10^{-14} . Dividing this value by 55.5 (the number of moles of water in 1 L of water) gives a K_a of 1.8×10^{-16} and puts water on the same concentration basis as the other substances in the table. A paper in the May 1990 issue of the *Journal of Chemical Education* (p. 386) outlines the justification for this approach. For a dissenting view, see the March 1992 issue of the *Journal of Chemical Education* (p. 255).

PROBLEM 4.8 As noted in Problem 4.7, hydrogen cyanide (HCN) has a pK_a of 9.1. Is cyanide ion (CN^-) a stronger base or a weaker base than hydroxide ion (HO^-)?

In any proton-transfer process the position of equilibrium favors formation of the weaker acid and the weaker base.

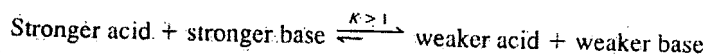
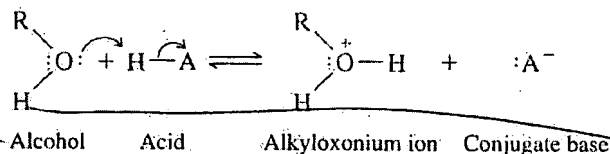


Table 4.2 is set up so that the strongest acid is at the top of the acid column, with the strongest base at the bottom of the conjugate base column. An acid will transfer a proton to the conjugate base of any acid that lies below it in the table, and the equilibrium constant for the reaction will be greater than one.

Table 4.2 contains both inorganic and organic compounds. Organic compounds are similar to inorganic ones when the functional groups responsible for their acid-base properties are the same. Thus, alcohols (ROH) are similar to water (HOH) in both their Brønsted acidity (ability to donate a proton from oxygen) and Brønsted basicity (ability to accept a proton on oxygen). Just as proton transfer to a water molecule gives oxonium ion (hydronium ion, H_3O^+), proton transfer to an alcohol gives an alkyloxonium ion (ROH_2^+).

This is one of the most important equations in chemistry.



We shall see that several important reactions of alcohols involve strong acids either as reagents or as catalysts to increase the rate of reaction. In all these reactions the first step is formation of an alkyloxonium ion by proton transfer from the acid to the oxygen of the alcohol.

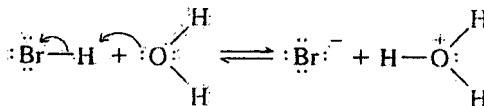
PROBLEM 4.9 Write an equation for proton transfer from hydrogen chloride to *tert*-butyl alcohol. Use curved arrows to track electron movement, and identify the acid, base, conjugate acid, and conjugate base.

PROBLEM 4.10 Is the equilibrium constant for proton transfer from hydrogen chloride to *tert*-butyl alcohol greater than 1 or less than 1?

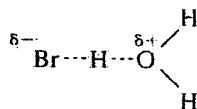
Alkyl halides are neither very acidic nor very basic and are absent from Table 4.2. In general, compounds, including alkyl halides, in which all the protons are bonded to carbon are exceedingly weak acids—too weak to be included in the table.

4.7 ACID-BASE REACTIONS: A MECHANISM FOR PROTON TRANSFER

Potential energy diagrams of the type used in Chapter 3 to describe conformational processes can also help us understand more about chemical reactions. Consider the transfer of a proton from hydrogen bromide to water:



A potential energy diagram for this reaction is shown in Figure 4.6. Because the transfer of a proton from hydrogen bromide to water is exothermic, the products are placed lower in energy than the reactants. The diagram depicts the reaction as occurring in a single **elementary step**. An elementary step is one that involves only one transition state. A reaction can proceed by way of a single elementary step, in which case it is described as a **concerted** reaction, or by a series of elementary steps. In the case of proton transfer from hydrogen bromide to water, breaking of the H—Br bond and making of the H₂O—H bond occur “in concert” with each other. The species present at the transition state is not a stable structure and cannot be isolated or examined directly. Its structure is assumed to be one in which the proton being transferred is partially bonded to both bromine and oxygen simultaneously, although not necessarily to the same extent.



Dashed lines in transition-state structures represent **partial bonds**, that is, bonds in the process of being made or broken.

The molecules undergo a chemical

is bimolecular reaction with a molecule of water.

PROBLEM 4.1 Write an equation for the transfer of a proton from hydrogen bromide to water.

Proton transfer is the most rapid chemical reaction between two molecules. The activation energy for this reaction is very low.

The concentration of water is so high that the reaction is first order in water. The cost of breaking the H₂O—H bond is small. The reaction proceeds in a single stepwise process followed by a concerted process.

4.8 PREPARATION OF ALKYL HYDRIDES

Much of what we know about the pharmacology of disease. Agricultural products used for the synthesis of pharmaceuticals are especially important.

The process of an alcohol is

4.8 Preparation of Alkyl Halides From Alcohols and Hydrogen Halides

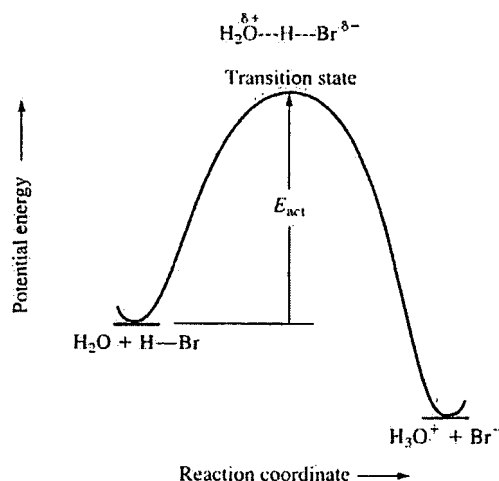
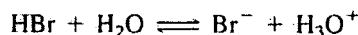


FIGURE 4.6
Potential energy diagram for concerted
molecular proton transfer
from hydrogen bromide to
water.

The **molecularity** of an elementary step is given by the number of species that undergo a chemical change in that step. The elementary step



is **bimolecular** because it involves one molecule of hydrogen bromide and one molecule of water.

PROBLEM 4.11 Represent the structure of the transition state for proton transfer from hydrogen chloride to *tert*-butyl alcohol.

Proton transfer from hydrogen bromide to water and alcohols ranks among the most rapid chemical processes and occurs almost as fast as the molecules collide with one another. Thus the height of the energy barrier separating reactants and products, the **activation energy** for proton transfer, must be quite low.

The concerted nature of proton transfer contributes to its rapid rate. The energy cost of breaking the H—Br bond is partially offset by the energy released in making the H₂O—H bond. Thus, the activation energy is far less than it would be for a hypothetical stepwise process involving an initial, unassisted ionization of the H—Br bond, followed by a combination of the resulting H⁺ with water.

4.8 PREPARATION OF ALKYL HALIDES FROM ALCOHOLS AND HYDROGEN HALIDES

Much of what organic chemists do is directed toward practical goals. Chemists in the pharmaceutical industry synthesize new compounds as potential drugs for the treatment of disease. Agricultural chemicals designed to increase crop yields include organic compounds used for weed control, insecticides, and fungicides. Among the “building block” molecules used as starting materials to prepare new substances, alcohols and alkyl halides are especially valuable.

The procedures to be described in the remainder of this chapter use either an alkane or an alcohol as the starting material for preparing an alkyl halide. By knowing how to

The 1967 Nobel Prize in chemistry was shared by Manfred Eigen, a German chemist who developed novel methods for measuring the rates of very fast reactions such as proton transfers.